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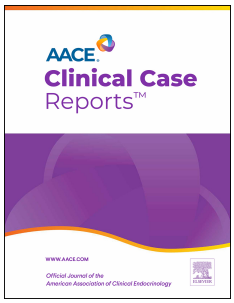

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Thyroiditis after Coronavirus Disease 2019 (COVID-19) mRNA Vaccine: A Case Series

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ABSTRACT

Background: While SARS-COV-2 virus infection was reported to cause subacute thyroiditis, the mRNA vaccine for SARS-COV-2 was suspected to induce thyroiditis with thyrotoxicosis.

Case Report: We describe three patients without a history of thyroid disease who presented with symptomatic, biochemical, and radiological evidence of thyroiditis with thyrotoxicosis, 10-20 days after receiving either the Pfizer Bio-NTech or the Moderna COVID-19 mRNA vaccine. All presented with thyrotoxicosis, but with negative thyroid stimulating immunoglobulins for Graves' disease and no autonomous nodules. Two patients underwent thyroid uptake and scan which confirmed thyroiditis. One patient had significantly increased erythrocyte sedimentation rate (ESR) and Interleukin-6 (IL-6). All had improvement in symptoms with non-steroidal anti-inflammatory drugs (NSAIDs), with one patient eventually requiring steroids for symptom control.

Discussion: The mRNA vaccine for SARS-COV-2 was associated with thyroiditis and presented with thyrotoxicosis. Elevated proinflammatory markers and cytokines after vaccines may play a major role.

Conclusion: Our case series report highlights a possible relationship between the COVID-19 mRNA vaccine and thyroiditis with thyrotoxicosis, which previously not recognized by health providers.

Key words: Subacute Thyroiditis, COVID-19, mRNA vaccine

INTRODUCTION

Subacute thyroiditis (SAT) is an inflammatory disease of the thyroid and a common cause of thyrotoxicosis. It is normally characterized by an enlarged tender thyroid gland with referred pain to the jaws and ear, biochemical evidence of thyrotoxicosis, elevated inflammatory markers such as ESR and C-reactive protein (CRP), and decreased radioactive iodine uptake. It is usually caused by infections with various viruses (1). More recently, there have also been case reports of SAT due to SARS-COV-2 infection (2).

While viruses are the main etiology of SAT, there have been rare cases reports of SAT following immunizations, such as the influenza vaccine (3). These rare cases have so far only been reported in patients receiving immunizations containing viral antigens. Recently, two pharmaceutical companies, Pfizer Bio-NTech and Moderna developed mRNA vaccines for SARS-COV-2. Unlike the influenza vaccine, which exposes the body to viral antigens directly, the mRNA vaccines work by instructing the cells to synthesize viral proteins and thereby trigger the immune system to produce antibodies. With the universal use of mRNA vaccines, the possible side effects will be discovered. SAT induced by mRNA vaccines for SARS-COV-2 have been recently reported but remains a less well-recognized phenomenon (4,5). We report three cases of thyroiditis with thyrotoxicosis following the mRNA vaccine for SARS-COV-2.

CASE REPORT

Patient #1:

a 37-year-old Indian male patient with a history of prediabetes and dyslipidemia presented to Emergency Department with fevers and neck pain. The patient had received his first dose of

Moderna mRNA COVID-19 vaccine about 15 days before presentation. In ER, his vital signs were significant for tachycardia with a heart rate of 125 bpm. Physical exam was significant for an enlarged, tender thyroid gland, without proptosis. ER work-up also showed significantly increased ESR and IL-6 with negative COVID-19 PCR test. While presenting as hyperthyroid, he underwent a radioactive iodine uptake scan showing decreased uptake with a 4-hour uptake of 0.4% and a 24-hour uptake of 0.01%, consistent with thyroiditis. The patient was initially started on treatment with propranolol and ibuprofen. However, after 3 days his symptoms of neck pain continued; therefore, ibuprofen was discontinued, and a prednisone taper was started which subsequently alleviated his symptoms.

Patient #2:

a 35-year-old Indian male with unremarkable medical history presented to the clinic with complaints of palpitations and neck pain. He had received his first dose of Pfizer-BioNTech mRNA COVID-19 vaccine about 10 days before presentation. Physical examination was significant for tachycardia with a heart rate of 130 bpm and anterior neck tenderness. He was started on propranolol and ibuprofen which alleviated his symptoms. Two weeks after the initial visit, repeated thyroid function improved with trending down free thyroxine (T4) and total triiodothyronine (T3) without any thyroxine production inhibition therapy, which was supportive for a clinical diagnosis of SAT.

Patient #3:

a 41-year-old Indian female patient with an unremarkable past medical history was referred to Endocrinology for hyperthyroidism and tachycardia. She had received her second dose of

PfizerBioNTech vaccine 20 days prior. She recalled no other symptoms except palpitations after the first dose; however, she reported worsening palpitation after the second dose. In clinic she was found to be tachycardic with a heart rate of 110 bpm. With clinical hyperthyroid, the radioactive iodine thyroid uptake scan revealed a 4-hour uptake of 1.4% and 24-hour uptake of 0.6%, suggestive of thyroiditis. She was managed with diltiazem and ibuprofen.

Lab work showed normal CBC and CMP for all three patients. Additional lab results including thyroid stimulating hormone (TSH), free T4, total T3 and ESR are shown in **Table 1**. Thyroid antibodies were negative including thyroid stimulating immunoglobulin (TSI), thyroid peroxidase (TPO), and anti-thyroglobulin (**Table 1**). Thyroid ultrasound in all three patients showed a heterogeneous and enlarged thyroid gland without nodules (**Figure 1**).

DISCUSSION

Cases of patients who developed SAT after SARS-COV-2 mRNA vaccine have recently been reported (4,5). Iremli et al. reported three female cases who developed SAT a few days after mRNA vaccines for COVID-19 in Europe (4), while Schimmel et al. reported one similar case in the USA (5). The common clinical features are middle age, no thyroid disease history, development of thyrotoxicosis with neck tenderness 4-27 days after the first or second dose, and negative thyroid antibodies (TSI, TPO, and anti-thyroglobulin). Thyroid ultrasound showed enlarged heterogeneous thyroid glands with no nodules and decreased uptake.

Patients with SAT typically present with neck tenderness caused by thyroid gland inflammation. Key clinical features of SAT is an elevated level of ESR and CRP (6) and neck pain relieved by

NSAID or steroids. Additionally, color flow doppler ultrasonography of the thyroid gland shows an enlarged heterogeneous gland with low to normal vascularity (7). Another hallmark of the disease is a low thyroid uptake of radioactive iodine. The peak incidence occurs around 30-50 years of age and women are more frequently affected than men (8). Previous studies have also shown the susceptibility of SAT in patients with certain types of human leukocyte antigen such as HLA-B35 (9).

Our three patients, at middle age, 2 male and one female, developed symptomatic hyperthyroidism with biochemical evidence of thyrotoxicosis after receiving either the Moderna or Pfizer-BioNTech vaccines, within 10-20 days after the first or second dose. Work-up for Graves' disease and autonomous nodule was negative. Patient #1 and Patient #3 had decreased radioactive iodine uptake scans which confirmed thyroiditis, for which the differential diagnosis includes SAT and Hashitoxicosis. Although all three patients had negative TPO and anti-thyroglobulin, there is still a small possibility that they may have baseline antibody-negative chronic thyroiditis exacerbated by the COVID-19 mRNA vaccine.

The mechanism by which the vaccine causes thyroiditis remains unclear due to limited data. While immune reactivity to viral antigens has been thought to be a plausible mechanism in cases of SAT following influenza vaccinations, there may be a different mechanism at play in patients receiving mRNA vaccinations. In a prior single-center study, patients infected with SARS-COV-2 who developed thyrotoxicosis were found to have elevated IL-6 levels (10). This study indicated that COVID-19 may be associated with a high risk of thyrotoxicosis in relationship with systemic immune activation and cytokine storm induced by the SARS-CoV-2 infection.

Previous reports have also shown that interferon and ribavirin therapy-induced thyrotoxicosis (11). In our study, Patient #1 had significantly increased IL-6 level. These studies suggested a possible role of cytokine in mRNA vaccine-induced SAT.

Our cases showed the latency period is about 10-20 days after the vaccine injection (1st or 2nd), and we will follow up to monitor the disease course for the hyperthyroidism phase, hypothyroidism phase, and recovery phase. It is not clear whether mRNA-induced SAT has a different disease course compared to the other common virus-induced SAT.

Although most cases of SAT are self-limiting, the recommended approach is to start symptomatic therapy for heart rate control and NSAIDs for neck pain as needed in mild cases, or steroids reserved for severe cases (12). Although specific data on the efficacy of COVID-19 vaccines in the setting of glucocorticoids administration are lacking, studies showed decreased efficacy of other virus vaccines after glucocorticoid administration, like influenzas (13). In mRNA vaccine administration, the expressed S antigen (spike protein) elicits an immune response, including both antibody and T cell responses, to protect against COVID-19 (14); however, systemic glucocorticoids have been considered as immunosuppressive therapy, which can suppress T helper cells, which modulate antibody class switching (15). Fauci et al. found IV hydrocortisone (400 mg) administration decreased circulation of T cells within 48 hours (16). Therefore, in mRNA vaccine-induced SAT, glucocorticoids use should be cautious, since it might interfere with the protective antibodies production induced by vaccinations.

In addition, it is unclear whether mRNA-vaccine-induced SAT is associated with younger age since data from the age group of 12-16 years are very limited. The mRNA vaccine has been approved for adolescents (age of 12-16) by FDA. In this age group, thyroid hormone plays a critical role in physical growth and sexual/mental development. Undiagnosed thyroiditis could cause certain medical, psychological, and social disorders which affect growth and development during puberty (17). The potential effects of the mRNA vaccine on adolescent growth and development are unknown, therefore health care provider index of suspicion and patient education are important.

A limitation of our series is the small number of patients. It would be interesting to see the incidence of this phenomenon in the future as more people start to get SARS-COV-2 vaccines.

CONCLUSION

In summary, we reported three cases of thyroiditis with thyrotoxicosis occurred in 1-4 weeks after receiving the first or second dose of mRNA COVID vaccines, indicating a possible relationship between SAT and mRNA COVID immunization. Symptom control with Beta-blocker and NSAIDs are usually recommended as glucocorticoids might interfere with vaccine-induced protective antibody production. With an increase in the number of immunizations, further data will provide more insight for future clinical care decisions.

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206 **Figure Legends:**

207 **Figure 1.** Transverse ultrasound images of the thyroid gland in all three patients showing a

208 heterogeneous and enlarged thyroid gland without nodules

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229 **Table 1.** Demographic characteristics, lab results and imaging findings of all three patients

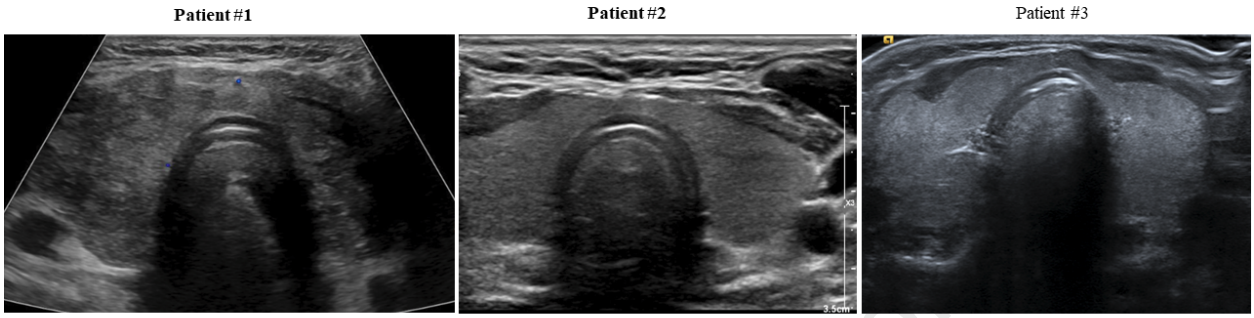
Characteristics	Patient #1	Patient #2	Patient #3
Age, y	37	35	41
Gender	Male	Male	Female
BMI, kg/m^2	26	28.4	21
COVID-19 vaccine	Moderna	PfizerBioNTech	PfizerBioNTech
Onset of symptoms	15 days after 1st dose	10 days after 1st dose	20 days after 2nd dose
Heart rate, bpm	125	130	110
Treatment	Propranolol, Ibuprofen and Prednisone	Propranolol and ibuprofen	Cardizem and ibuprofen
TSH (mIU/ml, NR: 0.45-4.5)	<0.01	0.07	0.019
Free T4 (ng/dL, NR: 0.82-1.77)	6.96	3.04	2.52
Total T3 (ng/dL, NR:76-181)	328	200	233
TSI	Negative	Negative	Negative
TPO	Negative	Negative	Negative
Anti-thyroglobulin	Negative	Negative	Negative
ESR (mm/hr, Ref: 0-10)	51	NA	NA
IL-6 (pg/mL, NR: ≤ 1.8)	13.2	NA	NA
Radioactive iodine thyroid uptake scan (NR: 4-hour, 5-15%; 24-hour, 15-35%)	4-hour, 0.4% 24-hour, 0.01%	NA	4-hour, 1.4% 24-hour, 0.6%

230 **Abbreviation:** BMI, body mass index; ESR, Erythrocyte sedimentation rate; IL-6, Interleukin-6;

231 TPO, Thyroid Peroxidase; TSH, thyroid stimulating hormone; TSI, thyroid stimulating

232 immunoglobulin; T3, triiodothyronine; T4, thyroxine; NA, not available; NR: normal range

Figure 1



Highlights

Teaching points:

1) Thyrotoxicosis with palpitation, and neck tenderness is the most common presentation of thyroiditis. The patients with new onset of thyrotoxicosis should be asked about history of mRNA-vaccine injection for the possible etiology.
2) mRNA vaccine induced thyroiditis could occur 10-20 days after the first dose or the second dose.
3) Management is to relieve the symptom of tachycardia with beta-blocker and neck pain with NSAIDS. Glucocorticoid steroid is used with caution or avoided when possible because of the concern about interfere with vaccination induced protective antibody production.
4) It is unclear whether mRNA vaccine induced thyroiditis is age-related, although all three cases are at middle-age.

Clinical Relevance

The healthcare providers should be aware of this side effect and manage it in a prompt and proper way, so patients would not be reluctant to receive the mRNA COVID-19 vaccines. Thyroid hormones play a very import role in adolescents, and pregnant women. Healthcare providers should be alert about the possible SAT development.

Disclosure

The authors have no multiplicity of interest to disclosure.